REMARKS

Claims 6-16 and 47-78 are pending in the current application. Claims 6-10, 47 and 48 have been allowed. Reconsideration of the present application in view of the following remarks is respectfully requested. Upon entry of these amendments, claims 6-16 and 47-78 will be pending. Support in the specification for amended claims 10, 12, 15, 16, 53-55, and 62-69, and new claims 70-78, may be found in the specification as shown in the following table:

Claim	Support in specification
50	Claim 12;
51	Previous claim 51;
60	Page 17, lines 5-28; page 16 line 20 to page 17, line 4
61	Page 17, lines 5-28; page 16 line 20 to page 17, line 4
62	Page 18, lines 8-13; page 16 line 20 to page 17, line 4;
63	Page 18, lines 8-13; page 16 line 20 to page 17, line 4;
66	Page 15, lines 21-27;
67	Page 15, lines 21-27;
68	Page 15, line 27 to page 16, line 2;
69	Page 15, line 27 to page 16, line 2;
74	Page 16, lines 11-12; pate 17, lines 5-19;
75	Page 16, lines 11-12; page 18, lines 8-13; Example 5.C;
77	Page 16, lines 11-12; page 15, line 21 to page 16, line 2;
78	Page 16, lines 11-12; page 15, line 21 to page 16, line 2.

As set forth above, these claim amendments and new claims are supported by the specification, and no new matter has been introduced.

Claims 50 and 51 have been amended to more distinctly point out the subject matter of the Applicants' invention. Per the Examiner's suggestion, claim 50 has been amended to include the limitations of claim 12. This amendment should obviate the Examiner's objections to claim 50 and to claim 51, which depends upon claim 50. Applicants do not, however, by this amendment admit that claim 12 is not patentable. Claims 60, 61 and 74 have been amended to recite the conditions under which an agent is identified as a modulator

of the level or activity of a protein produced by a dorsal root ganglion cell. Claims 62, 63 and 75 have been amended to recite the particular response to be detected. Claims 66, 67 and 77 have been amended to identify how cell death is to be quantified. Finally, claims 68, 69 and 78 have been amended to clarify the determination of an agent that affects dorsal root ganglion cell death.

Entry of the foregoing amendments and remarks into the file of the above-referenced patent application is respectfully requested. Applicants believe that each ground for rejection has been successfully overcome or obviated. After entry of this amendment, Claims 6-16 and 47-78 will be pending. Claims 6-10, 47 and 48 have been allowed. Furthermore, because the Examiner has not rejected or objected to claim 53 on any basis, this claim should also be allowed. For the reasons stated above, Applicants believe that the claims are now in condition for allowance.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 60-63, 66-69, 74, 75, 77 and 78 under 35 U.S.C. § 112, second paragraph. Claims 60-63, 66-69, 74, 75, 77 and 78 as amended should now be in condition for allowance.

The Examiner believes that claims 60, 61 and 74 are indefinite in their recitation of "measuring the ability of the candidate agent to modulate the activity of a protein produced by a cell" because is it unclear what type of measurement is being referred to. Office Action, page 4. Applicants have amended the claim to delete the quoted language and recite that, where the level or activity of a protein in the presence of the agent is different than the level or activity in the agent's absence, the agent is identified as a modulator of the protein's activity. Applicants respectfully submit that these claims as amended are definite, and request withdrawal of the rejection on this basis.

The Examiner also believes that claims 62, 63 and 75 are indefinite in their recitation of "detecting a response or lack of response in a cell" because it is unclear what type of response is to be detected. Office Action, page 4. Applicants have amended claims 62, 63 and 75 to recite that the response is selected from the group consisting of a change in the level of an mRNA in the cell, change in the level of a protein in the cell, or change in the activity of a protein in the cell. The Examiner also believes that the recitation of "wherein

said response is correlated with the presence of said protein" renders the claims indefinite. Office Action, page 4. Applicants have amended these claims to delete the quoted language. Applicants respectfully submit that these claims as amended are definite, and request withdrawal of the rejection on this basis.

The Examiner also believes that claims 66, 67 and 77 are indefinite in their recitation of "measuring the ability of the candidate agent to affect death of the cell" because it is unclear what type of measurements are made to measure cell death. Office Action, pages 4-5. Applicants have amended claims 66, 67 and 77 to recite that the number of cells dying in the presence of an agent is compared to the number dying in the absence of the agent, and that if the numbers differ, the agent is identified as an agent that affects dorsal root ganglion cell death. This comparison correlates the amount of cell death with the identification of the agent. Applicants respectfully submit that these claims as amended are definite, and request withdrawal of the rejection on this basis.

Finally, the Examiner believes that claims 68, 69 and 78 are indefinite in their recitation of "measuring the effect of the alteration on the death of the cell" because it is unclear what type of measurements are made to measure cell death. Applicants have amended claims 68, 69 and 78 to recite that the number of cells dying when the expression of a protein is altered is compared to the number dying when the expression of the protein is not altered, and that if the numbers differ, the protein is identified as a protein that regulates dorsal root ganglion cell death. Applicants respectfully submit that these claims as amended are definite, and request withdrawal of the rejection on this basis.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 12-16, 49, 52 and 54-78 under 35 U.S.C. § 112, first paragraph, for lack of enablement for the reasons advanced on pages 2-4 of the Office Action of Paper No. 19 ("Paper No. 19").

Applicants note that in Paper No. 19, the Examiner rejected only claims 54-69 on this basis and did not reject claims 12-16, 49 and 52, directed to conditionally-immortalized dorsal root ganglion progenitor cells and neurons. Thus, with respect to the new enablement rejection of claims 12-16, 49 and 52, the Examiner has not provided the basis for this rejection stated in the instant Office action or in Paper No. 19. Applicants respectfully point

out that the Examiner's bases for rejection set forth Paper No. 19 are inapplicable to these claims, because those bases of rejection were specific to the methods recited in claims 54-69, not the cells of the methods. Accordingly, it appears the present rejection of claims 12-16, 49 and 52 for lack of enablement may be an error.

In any event, it is clear that the conditionally-immortalized cells, and neurons differentiated therefrom, are enabled. The Examples provide a detailed account of the actual isolation of such cells, and the Detailed Description of the Invention provides additional methods of isolating such cells. Following the application's disclosure, anyone of skill in the art can make the cells, without undue experimentation and with excellent prospects for success. Applicants therefore submit that claims 12-16, 49 and 52 are fully enabled, and request that the Examiner withdraw the rejection of these claims on this basis.

The Examiner believes that there is an insufficiently enabling disclosure for claims 54-59, directed to methods of transplanting conditionally-immortalized dorsal root ganglion progenitor cells into a mammal. Applicants respectfully disagree, and assert that the claims are adequately enabled for the following reasons.

The Examiner, in Paper No. 19, cites Jackowski *et al.* as allegedly establishing the limitations and unpredictability associated with the transplantation of neural tissue. The inapplicability of this reference was demonstrated in Applicants' September 9, 2002 amendment ("Paper No. 33"). Jackowski *et al.* is directed to the failure of *CNS*, not *PNS* neural regeneration.

The Examiner appears to believe that the only asserted utility for transplanting the cells is to provide a therapeutic benefit. With respect, Applicants point out that the asserted utility is broader. The specification states that "the PNS progenitor cell lines described herein may be used *in vivo*, in transplantation studies . . . Studies may address the differentiation of the cells when transplanted into the developing or adult PNS." Page 18, lines 14-18. These studies clearly encompass research on the transplanted cells themselves, as part of basic science, and are not limited to research solely directed to therapeutic regimens.

The arguments presented above for claims 54-59 apply as well to claims 70-73, which differ only in that they are directed to the use of differentiated cells as opposed to conditionally-immortalized progenitor cells.

The Examiner also believes that there is an insufficiently enabling disclosure for claims 60, 61 and 74, directed to methods for screening for an agent that modulates the activity of a protein produced by a dorsal root ganglion cell. The Examiner asserts that "it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." Office action, page 4. For this proposition, the Examiner cites *Genentech, Inc. v. Novo Nordisk A/S*, 42 U.S.P.Q..2d 0105 (Fed. Cir. 1997).

Genentech is inapposite because the method at issue in that case, the use of cleavable fusion expression of hGH, was *not* generally known in the art; thus, the specification in that case, which only suggested several proteases to use, did not sufficiently describe the method. Indeed, the proteases Genetech relied on in that case had not been used by persons of skill in the art for the purpose Genentech was claiming. Here, however, the specification provides the novel aspect of the methods - the cells of the invention - and points the person of skill in the art to very well-known techniques, such as the determinations of mRNA or protein levels, for the remainder of the methods. Applicants respectfully submit that the Examiner has overlooked the novel aspect of these claims (and the other method claims): the conditionally immortalized dorsal root ganglion cells and the neurons differentiated from them.

The specification is enabling because, for the non-novel aspects of the invention, it refers to techniques that are well-known in the art. A specification is enabling where it, and the relevant art, would allow a person of skill in the art to practice the invention without undue experimentation. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The specification states that a conditionally-immortalized (*i.e.*, undifferentiated) PNS cell line may be used to screen for agents that modulate the activity of a PNS cell protein. (Page 17, lines 5-7). The specification states that the modulation of a protein by a compound may be assessed by examination of the tested compound's effect on transcription, translation, or the activity of the protein itself. (Page 17, lines 5-19.) Determination of each utilizes art that was well-known at the time the application was filed. For example, modulation of transcription was widely known to be assessable using RT-PCR, Northern blots, and dot- or slot-blots. For translational modulation, it was well-known that one could compare the amount of a specific protein produced (detectable, *e.g.*, by antibodies, immunoassays, protein gels or western blots) to the amount of mRNA produced. For

modulation of protein activity, specific targets, such as ion channels, neurotransmitter receptors and transporters, were well-known, as were the means for assessing their activities. Indeed, such targets have been the focus of a number of drug screens. The techniques known in the art presented no problems of undue experimentation, as each encompasses standard laboratory procedures. Thus, the art itself presented the parameters to measure to determine whether a specific compound modulates the activity of a protein produced by a dorsal root ganglion cell.

The Examiner further believes that claims 62, 63 and 75 are not supported by an enabling disclosure because "the specification does not teach what type of response must be detected or how it is to be detected." Paper No. 19, page 4. Applicants have amended claims 62, 63 and 75 to recite that the response is a change in the level of an mRNA, change of level of a protein, or change of the activity of a protein in a cell. This comports with the specification's teachings. For example, Example 4 discloses the determination that certain ion channels are present in a cell by examining the changes in sodium current when cells are contacted with an inhibitor, TTX. (Page 30, lines 4-16). The presence of certain N-, L- and P-type channels may be assessed by contacting cells with ω-CTX-GVIA, nimodipine, or ω-Aga-IVA, respectively, and assessing changes in calcium currents. (Page 31, lines 4-9; FIG. 23.) The presence of capsaicin receptors can be assessed by contacting cells with capsazepine and noting any change in capsaicin-mediated current. (Page 31, lines 23-27; FIG. 26). The specification also discloses that differential display may be used to assess the response of the cell. (Page 18, lines 8-13.) Thus, changes in gene expression or in the level of a protein may be the response contemplated by these claims. Differential display, of either proteins or of mRNA, was well-known in the art at the time of filing, and a change in gene expression is a well-known "response" of a cell correlated to the presence of an external factor. It follows that the presence of a protein in a sample can be assessed by contacting the cell with a sample which may contain the protein, and assessing a change in gene expression, protein production, or in specific, measurable currents in the cell. Thus, the specification enables the methods of claims 62, 63 and 74. Applicants respectfully request the Examiner withdraw the rejection of these claims on this basis.

The Examiner further believes that claims 64, 65 and 76, directed to methods of identifying a human dorsal root ganglion gene or protein, are insufficiently enabled. The

Examiner provides no specific argument that these claims are non-enabled. Applicants respectfully disagree, and assert that the claims are enabled for the following reasons. The specification states that the presence of a nucleic acid sequence, such as a gene, may be determined through standard techniques such as PCR or hybridization techniques, such as are discussed in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual* (cited in the specification). (Page 16, lines 22-26). These techniques have been extensively reported and described in the art; thus, there is no need for the specification to replicate them. The only parameters required for "identification" according to the claim is a determination as to whether a PCR product has been produced, or hybridization has taken place.

The specification further states that a particular protein may be detected by an antibody, *e.g.*, in an immunoassay such as those described extensively in Harlowe and Lane, *Antibodies: A Laboratory Manual* (cited in the specification). (Page 16, line26 - page 17, line 4). Again, the only parameter required is a determination that a particular antibody has bound its intended target; methods of such determinations were well-known in the art and disclosed, *inter alia*, in the references cited in the specification. Applicants therefore respectfully assert that, because Applicants have provided the novel aspect of the claims, the cells of the invention, claims 64, 65 and 76 as amended are, in view of the state of the art, sufficiently enabled by the specification. Applicants respectfully request the Examiner withdraw the rejection of these claims on this basis.

Finally, the Examiner believes claims 66-69, 77 and 78, directed to methods of identifying agents that modulate cell death, or proteins that regulate cell death, are insufficiently enabled. Applicants have amended these claims to recite the specific conditions under which such agents or proteins are identified. The specification discloses that apoptosis, *i.e.*, cell death, is brought about by, *inter alia*, withdrawal of growth factors. (Page 16, lines 21-27.) Evaluation of the effect of a candidate agent on apoptosis is evaluated simply by assessing the percentage of neurons that die (undergo apoptosis) in the presence and absence of the agent. Such techniques were known in the art. For example, Ferrer-Montel *et al.*, "Selected Peptides Targeted to the NMDA Receptor Channel Protect Neurons from Excitotoxic Death," *Nat. Biotech.* 16:286-291 (March, 1998) assessed the ability of small defined peptides to block the apoptotic effect of the NMDA receptor by exposing cells to NMDA (which induces apoptosis) in the absence or presence of the peptides, then

determining the percentage of cells that survived. Again, given the novel cells of the invention and the state of the art at the time of filing, claims 66, 67 and 77, as amended, are enabled.

Applicants have similarly amended claims 68, 69 and 78, directed to methods of screening for a protein that regulates dorsal root ganglion cell death. Again, given the novel cells of the invention, the state of the art supports enablement of these claims. Techniques for the modulation of the level of expression of a particular protein were well known at the time the application was filed, and include antisense technology (demonstrated to work well in cell culture systems); site-directed mutagenesis; insertion of regulatable promoters into the genome; and transfection of expression vectors from which a particular protein may be overexpressed. Having such techniques in hand, it would have been straightforward for a person of skill in the art to modify the expression of a protein, and subsequently measure the effect of such an alteration on the number of cells that die. As noted above, persons of skill in the art were aware of techniques to induce apoptosis, such as withdrawal of growth factors (as cited by the specification; *see* page 16, lines 1-2) or addition of particular compounds. Thus, the specification, in light of the art at the time of filing, enables claims 68, 69 and 78 as amended. Applicants respectfully request the Examiner withdraw the rejection of these claims on this basis.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants' claims as amended should proceed to allowance. No fee, other than for the extension of time, is believed due. However, if a fee is deemed to be required in connection with this paper, please charge Pennie & Edmonds Deposit Account Number 16-1150 for the appropriate amount.

Respectfully submitted,

Date May 20, 2003

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EXAMINER
FALK, ANNE MARIE

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1632	37

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Resubmit Amendment 6/5/03 JW

Lawrence Graham

AMENDMENT CHECKLIST

(REVISED AMENDMENT FORMAT – VOLUNTARY PERIOD ONLY)

E

Application: 09060409
Legal Instruments Examiner: W. Phillips
Date of Amendment: 4-21-03

A review of applicant's amendment submitted under the revised amendment format reveals:

1. **The amendment fully complies with the voluntary revised amendment format.**

2. **Complete Claim Listing.** A complete listing of all of the claims is not present in the amendment paper.

- ☐ a. Applicant presents only currently amended claims.
- ☑ b. Applicant presents all claims except those claims, which are canceled.
- ☐ c. Applicant fails to present the text of all claims under examination.

☐ 3. **Ascending Order.** The claims of this amendment paper have not been presented in ascending numerical order.

☐ 4. **Status Identifiers.** No status identifiers (following each claim number) have been presented.

- ☐ a. Some status identifiers (following each claim number) have not been presented.
- ☐ b. Claims are presented with an incorrect or inconsistent status identifier.

  Claim(s) no. _____

☐ 5. **Separate Sheet.** Each section of the amendment does not begin on a separate sheet.

☐ 6. **Markings in Non-Amended Claims.** Claims not currently amended are marked up.

☐ 7. **Groupings.** Applicant has incorrectly grouped non-consecutive groups of canceled or withdrawn claims.

☐ 8. **Revised Format – Specification Only.** Only the specification is supplied using the revised amendment format. Applicant has submitted amendments to the claims using a clean version and a marked up version.

☐ 9. **Other** _____

RETURN THIS CHECKLIST TO THE TEAM LEADER.

***IF THE AMENDMENT FAILS TO COMPLY WITH THE VOLUNTARY REVISED AMENDMENT FORMAT, SUBMIT THIS CHECKLIST, THE AMENDMENT, & THE APPLICATION FILE TO THE TEAM LEADER.**

UNITED STATES PATENT AND TRADEMARK OFFICE

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Paper No. 37

Notice of Non-Compliant Amendment (Voluntary Revised Practice)

The amendment filed 4-21-03 under the voluntary revised amendment practice guidelines[1], published in the Official Gazette on February 25, 2003 (*Amendments in a Revised Format Now Permitted,* 1267 Off. Gazette 106), does not fully comply with minimal requirements of the voluntary practice. In order for the amendment to be entered, it must either (1) comply with the guidelines of the voluntary revised amendment practice (which practice invokes waivers of certain 37 CFR 1.121(a)-(d) requirements) or (2) comply with current 37 CFR 1.121 requirements.

THE FOLLOWING ITEM(S) IN APPLICANT'S AMENDMENT CAUSES THE AMENDMENT TO BE NON-COMPLIANT WITH THE VOLUNTARY REVISED AMENDMENT PRACTICE.

☑ 1. A complete listing of all of the claims is not present in the amendment paper.

☐ 2. The listing of claims does not include the text of all claims currently under examination.

☐ 3. The claims of this amendment paper have not been presented in ascending numerical order.

☐ 4. Each claim has not been provided with a status identifier, and, as such, the individual status of each claim cannot be determined.

☐ 5. Other: _____

_____

_____

LIE: Check one of the following boxes:

☐ **PRELIMINARY AMENDMENT:** Applicant is given ONE MONTH from the mail date of this letter to re-submit the amendment in compliance with either the guidelines of the revised amendment practice or current 37 CFR 1.121. Failure to comply with either the current 37 CFR 1.121 practice or with the voluntary practice will result in non-entry of the amendment and examination on the merits will commence without entry of the originally proposed preliminary amendment. This notice is not an action under 35 U.S.C. 132, and this ONE MONTH time limit is not extendable.

☑ **AMENDMENT AFTER NON-FINAL ACTION:** Since the above-mentioned reply appears to be a *bona fide* response, applicant is given a TIME PERIOD of ONE MONTH from the mailing of this notice within which to re-submit an amendment which complies with either the voluntary practice guidelines or current 37 CFR 1.121 in order to avoid abandonment. EXTENSIONS OF THIS TIME PERIOD ARE AVAILABLE UNDER 37 CFR 1.136(a).

[Signed by Team Leader]
Team Leader

[1] For further explanation of the guidelines of the revised amendment format, please see the posted notice and sample amendment format at:
http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf and
http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/formatrevamdtprac.pdf

March 26, 2003